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HAIR GROWTH AND TONIC AGENT

Inventors:

Norihei Nakamura
3-10-26-304 Sumiyoshihoncho
Higashinadaku, Kobe
Hyogo

Junichi Akiyama
4-8-18 Hiyodoridai
Higashinadaku, Kobe
Hyogo

Applicants:

593214017
Bimeeku K.K.
3-3-23 Kumauchibashi
Chuoku, Kobe

593214006
Nippon Soshia K.K.
3-4-4 Nishitenman
Kitaku, Osaka

Agents: ⬤   Ts⬤o Gaku, patent attorney, and
                                              two others

[There are no amendments to this patent.]

Abstract

Means to solve

Hair growth and tonic agent comprising one or more compounds selected from 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid and its derivatives, and (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives and blended therein.

Effect

The effects include no severe side effects as hormone-based agents; hair growth and tonic effects from the excellent scalp function enhancement by skin function stimulation; hair loss curing effects from the excellent rejuvenation of hair root cells.

Claims

1. Hair growth and tonic agent, characterized by comprising one or more compounds selected from 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid and its derivatives, and (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl] hept-5-enoic acid and its derivatives, as the effective component for hair growth acceleration.

2. Hair growth and tonic agent according to Claim 1, characterized by compounding one or more effective components for hair growth acceleration chosen from 13,14-dihydro-15-keto-9 (α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid and its derivatives.

3. Hair growth and tonic agent according to Claim 1, characterized by compounding one or more effective components for hair growth acceleration chosen from (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives.

4. Hair growth and tonic agent according to Claim 3, characterized in that the effective component for hair growth acceleration is chosen from (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid derivatives, especially (+)-isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate.

5. Hair growth and tonic agent according to any one of Claims 1-4, characterized in that besides the above effective components for hair growth acceleration, other known hair growth and tonic agents are also compounded.

6. Hair growth and tonic agent according to any one of Claims 1-4, characterized in that cyclodextrin is compounded for enhancing the stability of the above effective components for hair growth acceleration.

Detailed explanation of the invention

[0001]

Technical field of the invention

The present invention concerns hair growth and tonic agents based on effective components from the prostaglandin $F_2\alpha$ metabolite: 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid and its derivatives, and (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives, which are prostaglandin $F_2\alpha$ homologs, and similar metabolite-type prostaglandin related compounds, wherein such metabolites have no severe side effects as hormone-based agents but do have hair growth and tonic effects from the excellent scalp function enhancement by skin function stimulation and hair loss curing effects from the excellent rejuvenation of hair root cells.

[0002]

Prior art

There have been numerous studies of hormone agents, blood flow promoters, various cell activators, etc. in relation to prevention and cure of hair loss and hair growth and tonic action by stimulation of functions of the scalp and hair roots, and various effective components have been blended into topical hair growth agents. However, products having excellent effects as well as high safety have been few in number. Objective evaluation of effectiveness of some components shows that most of them show only preventive effects.

[0003]

Problems to be solved by the invention

It is an object of the present invention to develop hair growth and tonic agents displaying excellent safety and stability, hair loss curing effects with hair growth and tonic effects by the stimulation of the function of skin cells, promotion of healthier hair even for those without hair loss symptoms, highly preventive effects for hair loss, and prevention of aging of the scalp and hair roots.

[0004]

Means to solve the problems

The hair growth and tonic agents of the present invention are characterized by being compounded with one or more compounds selected from the prostaglandin $F_2\alpha$ metabolite: 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid and its derivatives, and (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives. Of the effective components of the present invention, (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives are preferred, while (+)-isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate is especially preferred. The effective components of the present invention are the metabolite-type prostaglandin homologs, which have metabolitic pathways similar to the intrinsic prostaglandin metabolitic pathway and display effectiveness in hair growth and tonic action.

[0005]

Prostaglandins biosynthesized in body tissues and organs are eicosanoids having various physiological roles, and it is generally considered that such actions are displayed via receptors. According to the prostaglandin types, the presence of prostaglandin D receptors (DP), prostaglandin E receptors (EP), prostaglandin F receptors (FP), prostaglandin I receptors (IP), thromboxane receptors (TP), etc., have been known. Thus, even in the tissues of hair root and scalp comprising epidermal cells and fibrocytes, prostaglandin production occurs and receptors are present according to some reports, thus it is obvious that they are deeply involved in dissociation and differentiation of cells of the scalp and hair root.
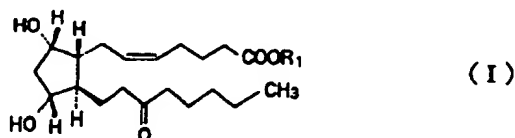
[0006]

Noting this point, we have carried out hair growth and tonic agent studies concerning various metabolite prostaglandins as pharmaceutically effective components over a long period of time. It was found that clinical hair loss symptoms occur with high frequency with an imbalance of the sympathetic nervous system and parasympathetic nervous system (sympathetic nerve dominance) in autonomic nerve control loss symptom [sic], thus we have carried out studies on hair growth using various sympathetic nerve blockers. For the first time, we discovered excellent hair growth effects of the above effective components of the present invention, which are sympathetic β blockers. Thus, the present invention is attained.

[0007]

Next, 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid and its derivatives which are effective components of the present invention are explained in detail. The prostaglandins considered for the present invention are prostanoic acids having OH groups at the 9α- and 11α-positions and can be shown by the formula (I) below:
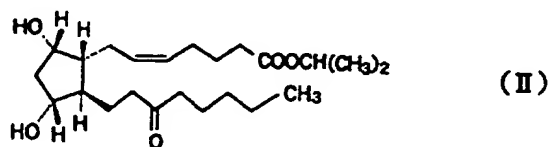
[Structure 1]

(I)

The compound represented by the formula (I) with R_1 being hydrogen atom (-H) is 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoic acid, and in its derivatives, R_1 may be an alkyl group such as methyl group ($-CH_3$), ethyl group ($-C_2H_5$), propyl group ($-C_3H_7$), etc., isoalkyl group such as isopropyl group ($-CH(CH_3)_2$), etc., or R_1 may be in the salt form with sodium, potassium, etc., or in the form of esters with aliphatic alcohols such as stearyl alcohol or sugar or polyhydroxy alcohols such as glucose, etc.

[0008]

For example, with R_1 being an isopropyl group, the compound is isopropyl 13,14-dihydro-15-keto-9(α),11(α)-dihydroxy-5-cis-13-trans-prostadienoate (isopropyl metabolite PGF2α, hereafter referred to as IPGF) having the structure (II) shown below:
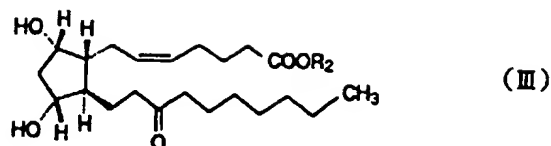
[Structure 2]

(II)

IPGF can be used in various formulations such as lotion, cream, etc.

[0009]

Specific examples of (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid and its derivatives are shown below. These effective components can be shown by the formula (III):
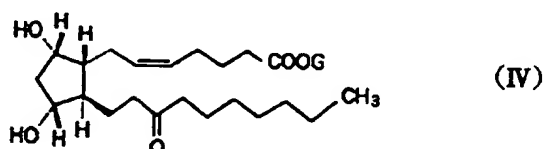
[Structure 3]

(Ⅲ)

The compound of formula (III) with R_2 being a hydrogen atom (-H) is unoprostone acid [sic], and in its other derivatives, R_1 may be an n-alkyl group such as methyl group (-CH_3), ethyl group (-C_2H_5), propyl group (-C_3H_7), etc., isoalkyl group such as isopropyl group (-CH(CH_3)_2), etc., or R_1 may be in a salt form with sodium, potassium, etc., or in the form of esters with aliphatic alcohols such as stearyl alcohol or sugar or polyhydroxy alcohols such as glucose, etc.

[0010]

For example, a unoprostone acid aglycone with the R_2 being glucose is (+)-glucopyranosyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (generic name: unoprostone acid glucoside, hereafter referred to as GIP), with the structure shown below:

[Structure 4]

(Ⅳ)

(In the formula, G represents glucose).

GIP can be used in various formulations such as lotions, creams, etc.

[0011]

Of the unoprostone acid derivatives, for the effective components of the present invention, (+)-isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (generic name: isopropyl unoprostone, hereafter referred to as IUP) is especially preferred. This compound can be represented by the formula (V) below:

[Structure 5]

(V)

IUP, with molecular weight 424.62, is an odorless, tasteless, colorless viscous liquid, freely soluble in ethanol or isopropyl alcohol, and also soluble in various oils used in topical agents, thus it can be used in various formulations such as lotions, creams, etc. The weight ratio of the effective component of the present invention to the hair growth and tonic agent (W/W) should be 0.0001-20% (W/W%), preferably 0.01-5.0%.

[0012]

While the mechanism of any action resulting in the effectiveness of the effective components of the present invention in the hair growth and tonic agents of the present invention is not clear yet, we assume that the hair growth and tonic effects result from the acceleration of the metabolic activity of cells with elevated enzyme activity related to cell dissociation and cornification. More specifically, it seems that sympathetic β blocking action of the effective components of the present invention, hair growth promotion action of the effective components of the present invention via the receptors in hair root cells and hair papillary [sic] cells, namely, promotion of transfer of nongrowth period to growth period of hair, growing period extension, promotion of dissociation and cornification of mother cells of growing hair, etc. can be contemplated. We have studied hair loss for a long time as well as the mechanism of action for a large number of effective components. As a result, the present invention is attained.

[0013]

The basic evaluation of the present invention is done with laboratory animals in terms of actions on the epidermal cells and hair mother cells. An experimental example is illustrated below.

[0014]

Experimental example

Hair was completely removed by the hand plucking method from a predetermined area (about 4 cm^2) of C3H male mice (8 weeks old) commonly used as laboratory animals for evaluation of effectiveness of hair growth. A solution of 0.05% IPGF, 2.0% GUP, 0.1% IUP in 60% aqueous alcohol, or 60% aqueous alcohol as the blank was applied to the dehaired area.

Application was carried out for two groups of 10 in total number (5 mice per group) until termination of hair regrowth, at a rate of 200 µL/day once a day for 27 days. 20 pieces of hair were removed from each animal on days 12, 14, 16, 20, 23, and 27 after the initiation of application, and were measured for actual length. Measured values were collected on a computer and subjected to statistical analysis to investigate the effectiveness. Results are given in Tables 1-3.

[0015]

Table 1

群 (匹数) Sample		1群 (5) 0.05% IPGF 被験液	4群 (5) 60%アルコール対照液
毛長平均 (mm) ±S.D 値	12日目	* 3.25±0.15	2.37±0.14
	14日目	* 4.81±0.18	4.20±0.27
	16日目	* 6.05±0.25	5.35±0.24
	20日目	* 6.99±0.24	6.46±0.19
	23日目	* 7.52±0.16	6.50±0.30
	27日目	* 7.45±0.19	6.83±0.15

Key: 1   Group (number of subjects)
2   Group
3   Sample solution
4   60% alcohol for blank
5   Hair length average
6   ± S.D. value
7   Day
8   *The significant difference below 1% in the significance level of the comparison of both groups with the alcohol blank group by statistical analysis (T test). Same hereafter.

[0016]

Table 2

群（匹数） Sample		2群（5） 0.1%ＧＵＰ　被験液	4群（5） 60%アルコール対照液
毛長平均（mm） ±S.D 値	12日目	＊　3.31±0.13	2.37±0.14
	14日目	＊　4.90±0.20	4.20±0.27
	16日目	＊　6.13±0.19	5.35±0.24
	20日目	＊　7.05±0.15	6.46±0.19
	23日目	＊　7.60±0.21	6.50±0.30
	27日目	＊　7.78±0.21	6.83±0.15

Key:
1   Group (number of subjects)
2   Group
3   Sample solution
4   60% alcohol for blank
5   Hair length average
6   ± S.D. value
7   Day

[0017]

Table 3

群（匹数） Sample		3群（5） 0.1%ＩＵＰ　被験液	4群（5） 60%アルコール対照液
毛長平均（mm） ±S.D 値	12日目	＊　3.30±0.10	2.37±0.14
	14日目	＊　4.80±0.15	4.20±0.27
	16日目	＊　6.01±0.23	5.35±0.24
	20日目	＊　6.98±0.19	6.46±0.19
	23日目	＊　7.41±0.20	6.50±0.30
	27日目	＊　7.46±0.22	6.83±0.15

Key:
1   Group (number of subjects)
2   Group
3   Sample solution
4   60% alcohol for blank
5   Hair length average
6   ± S.D. value
7   Day

[0018]

From the above experimental example, it is also learned that the components of the present invention have excellent hair starting and growth effects promoting the growth of hair [on the] scalp. The mechanism of this result seems that the effective components of the present invention penetrate into the skin, stimulate various activities of the cells of the scalp and hair root, promote the development of the hair capillary veins participating in increasing the hair growth, directly promote the function of skin cells, stimulate the state of the scalp, and promote hair growth.

[0019]

Composite actions are also investigated with materials known to have hair tonic effects, namely, promoting new hair and growth by the effective components of the present invention. Such materials are, e.g., (3-carboxypropyl)trimethylammonium chloride methyl ester, 6-amino-2,2-dihydrohydroxyimino-4-piperidinopyrimidine, 7-chloro-3-methyl-2H-benzo-1,2,4-thiadiazine-1,1-oxide, polyoxyethylene sorbitan monostearate (20 E.O.), Japanese green gentian extract, ethinyl estradiol, *Isodon japonicus* Hara extract, *kusan* extract, *saboten* extract, *nishiki* plant extract, urea, etc. As a result, synergetic effects are realized in new hair and hair growth. Composite actions are also studied with known skin stimulating components promoting skin blood flow, choline activating components, adrenaline suppressing component, muscle relaxing components, etc., in combination with the effective components of the present invention. Higher effectiveness is obtained.

[0020]

For increasing transdermal absorption of the effective components of the present invention, the topical agents of the present invention may also be compounded with humectants, softeners, surfactants, etc. Increased effects that are considered to occur due to increased absorption in the skin are observed. The content of the effective components of the present invention used in topical agents should be about 0.01-5.0%. The content of (3-carboxypropyl)trimethylammonium chloride methyl ester compounded in the hair growth and tonic agents containing 0.01-1.0% of the effective components of the present invention should be about 0.01-5.0%. The content of 6-amino-2,2-dihydrohydroxyimino-4-piperidinopyrimidine should be above 0.01-5.0%. The content of 7-chloro-3-methyl-2H-benzo-1,2,4-thiadiazine-1,1-oxide should be about 0.01-5.0%. The content of polyoxyethylene sorbitan monostearate (20 E.O.) should be 1.0-60.0%. The content of Japanese green gentian extract (dry weight 1 g corresponds to 1 g of extract) should be about 0.01-5.0%. The content of ethinyl estradiol should

be about 0.001-0.1%. The content of *Isodon japonicus* Hara extract (dry weight 1 g corresponds to 1 g of extract) should be about 0.01-10.0%. The content of *kusan* extract (dry weight 1 g corresponds 1 g of extract) should be about 0.01-10.0%. The content of urea should be about 0.1-10.0%.

[0021]

Cyclodextrins may be compounded for increased stability of the effective components of the present invention in the formulations. The cyclodextrin content may vary depending on the type of formulations, while addition of 0.1-50% (W/W) in the formulations shows excellent activity stabilization of the effective components.

[0022]

Application examples

Examples of the present invention is shown below. Besides the components of the present invention, other components known to be useful for the scalp and hair can also be compounded. The present invention is not limited to these examples. In the examples, the unit of the components used in the example is g (gram).

[0023]

Application Example 1

A cosmetic hair tonic gel with excellent tonic effect was prepared by the recipe shown below:

IPGF	0.5
7-Chloro-3-methyl-2H-1,2,4-thiadiazine-1,1-oxide	1.0
Concentrated glycerin	2.0
Ethylhexanediol	2.0
Hinokitiol	0.01
Decaglycerin monolaurate	0.5
Carboxyvinyl polymer	0.5
Cyclodextrin	1.0
Triethanolamine	as needed
Perfume	as needed
Alcohol	30.0
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

[0024]

Application Example 2

The recipe below was used to make a cosmetic hair tonic lotion in the conventional manner.

GUP	2.0
Concentrated glycerin	5.0
Salicylic acid	0.1
POE hardened castor oil (50 E.O.)	0.5
Alcohol	20.0
Perfume	small amount
Buffer	as needed
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

In the above recipe, POE is polyoxyethylene, and E.O. is ethylene oxide.

[0025]

Application Example 3

The recipe below was used to make a cosmetic hair tonic lotion in the conventional manner.

IUP	0.1
Kusan extract	5.0
Urea	1.0
β-Glycyrrhetinic acid	0.1
N-Lauroylglutamic acid sodium	0.5
Perfume	small amount
Buffer	as needed
Alcohol	50.0
Phenoxyethanol	1.0
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

[0026]

Application Example 4

IPGF	0.2
(3-Carboxypropyl)trimethylammonium chloride methyl ester	1.0
Concentrated glycerin	3.0
Isopropylmethylphenol	0.3
Decaglycerin monolaurate	0.5
Salicylic acid	0.5
Perfume	small amount
Buffer	as needed
Alcohol	40.0
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

[0027]

Application Example 5

GUP	2.0
6-Amino-1,2-dihydrohydroxyimino-4-piperidinopyrimidine	1.0
Concentrated glycerin	25.0
Salicylic acid	0.5
Polyoxyethylene hardened castor oil (50 E.O.)	0.5
Isopropylmethylphenol	0.3
Perfume	small amount
Buffer	as needed
Alcohol	60.0
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

[0028]

Application Example 6

A tonic shampoo was prepared from the recipe below in the conventional manner.

IUP	10.0
Lauryl POE (3) sulfate ester sodium salt	30.0
Lauryl sulfate sodium salt	15.0
Ethylene glycol monostearate	3.0
N-Lauroyldiethanolamide	2.0
Lanolin derivative	1.0
Hydrolyzed keratin	3.0
Cyclodextrin	5.0
Perfume	small amount
Color	small amount
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

In the above recipe, POE indicates polyoxyethylene.

[0029]

Application Example 7

A tonic rinse was prepared from the recipe below in the conventional manner.

IUP	5.0
Stearyltrimethylammonium chloride	2.0
Cetyl alcohol	2.0
Silicone oil	3.0
Oleyl POE (10) alcohol ether	1.0
Glycerin	5.0
Hydrolyzed keratin	2.0
Cyclodextrin	5.0
Perfume	small amount
Color	small amount
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g.)

In the above recipe, POE indicates polyoxyethylene.

[0030]

Experimental example

To a group of 4 healthy males of 36-51 years of age having hair loss symptom, about 3 mL were applied 1-2 times a day for 3 months to obtain the hair growth results shown below.

Evaluation standard

After 3 months, new hair growth in the application area was evaluated by the hair density measurement method by counting the number of hair stems in a unit area and SCORE method using photography. SCORE evaluation standards are given below:

SCORE 1: No hair at all, with only some soft hair.

SCORE 2: A number of soft hairs and some rigid hair in the hair loss area.

SCORE 3: Dense soft hair, with half being rigid hair.

SCORE 4: Entirely covered by rigid hair, but skin can be seen.

SCORE 5: Hair loss spot and thinning area are not visible at all.

An improvement of one rank or more by the SCORE evaluation is considered to be effective.

[0031]

Results

The hair growth agent from the base agent 1 compounded with 0.2% of IPGF showed an effectiveness of 78.5%. Similarly, the agent containing 2.0% of GUP showed an effectiveness of 75.9%. The agent containing 0.2% of IUP showed an effectiveness of 80.5%. The base agent 1 compounded with 1.0% of (3-carboxypropyl)trimethylammonium chloride methyl ester and 1.0% of IGPF showed a hair growth effectiveness 7.6% higher than the base agent 1 containing 1.0% of (3-carboxypropyl)trimethylammonium chloride methyl ester, indicating a synergetic effect by addition of IGPF.

[0032]

The base agent 2 compounded with 1.0% of 6-amino-1,2-dihydrohydroxyimino-4-piperidinopyrimidine and 0.5% of GUP showed a hair growth agent effectiveness 6.3% higher than the base agent 2 compounded with 1.0% of 6-amino-1,2-dihydrohydroxyimino-4-piperidinopyrimidine, indicating a synergetic effect by addition of GUP. The base agent 3 compounded with 1.0% of 7-chloro-3-methyl-2H-[benzo-1,2,4-thiadiazine]-1,1-oxide and 2.0% of IUP showed a hair growth agent effectiveness 10.8% higher than the base agent 3 compounded with 1.0% of 7-chloro-3-methyl-2H-[benzo-1,2,4-thiadiazine]-1,1-oxide, indicating a synergetic effect by addition of IUP.

[0033]

The base agent 1 compounded with 50% of polyoxyethylene sorbitan monostearate (20 E.O.) and 0.2% of IUP showed a hair growth agent effectiveness 7.9% higher than the base agent 1 containing 50% of polyoxyethylene sorbitan monostearate (20 E.O.), indicating a synergetic effect by addition of IUP. The water content in the base agent was subtracted equal to the amount of polyoxyethylene sorbitan monostearate (20 E.O.) used. The base agent 1 compounded with 1.0% of Japanese green gentian extract (corresponding to dry weight 1 g) and 0.2% of IUP showed a hair growth agent effectiveness 7.6% higher than the base agent 1 containing 1.0% of the Japanese green gentian extract (corresponding to 1 g of dry weight), indicating a synergetic effect by addition of IUP.

[0034]

The base agent 1 compounded with 0.01% of ethinyl estradiol and 0.2% of IUP showed a hair growth agent effectiveness 7.5% higher than the base agent 1 containing 0.01% of ethinyl estradiol, indicating a synergetic effect by addition of IUP. The base agent 1 compounded with 2.0% of *I. japonicus* extract (corresponding to 2 g dry weight) and 0.2% of IUP showed a hair growth agent effectiveness 4.4% higher than the base agent 1 containing 2.0% of *I. japonicus* extract (corresponding to 2 g dry weight), indicating a synergetic effect by addition of IUP. The base agent 1 compounded with 2.0% of urea and 0.2% of GUP showed a hair growth agent effectiveness 6.2% higher than the base agent 1 containing 0.2% of urea, indicating a synergetic effect by addition of GUP.

[0035]

Base agent 1 (unit: g)

Concentrated glycerin	3.0
Isopropylmethylphenol	0.3
Decaglycerin monolaurate	0.5
Salicylic acid	0.5
Perfume	small amount
Alcohol	40.0
Water*	to 100.0 g total

(*Water is added to make a total amount of 100.0 g. Same below.)

[0036]

Base agent 2	(unit: g)
Concentrated glycerin	25.0
Isopropylmethylphenol	0.3
Polyoxyethylene hardened castor oil (50 E.O.)	0.5
Salicylic acid	0.5
Perfume	small amount
Alcohol	60.0
Water	to 100.0 g total

[0037]

Base agent 3	(unit: g)
Concentrated glycerin	2.0
Isopropylmethylphenol	0.3
Decaglycerin monolaurate	0.5
Carboxyvinyl polymer	0.5
Triethanolamine	small amount
Ethylhexanediol	2.0
Perfume	small amount
Alcohol	30.0
Water	to 100.0 g total